

44  
cont'd  
coding for a fragment of said TBP-II which has the ability to inhibit the cytotoxic effect of TNF.

Claim 47, line 2, change "46" to --51--

#### REMARKS

Claims 11-14, 35-39 and 43-51 presently appear in this case. No claims have been allowed. Claims 14, 39, 45 and 50 have been withdrawn from consideration. The official action of February 26, 1999, and the reference relied upon therein has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to isolated DNA molecules which encode naturally occurring human TBP-II. TBP-II is a novel tumor necrosis factor binding protein which is an extracellular domain of a TNF receptor. It was first disclosed in the priority applications of the grandparent application, and one claim directed to this protein was officially found to be allowable by the examiner in charge of the parent case. The claims drawn to the protein in the parent application of 07/930,443 are now involved in an interference proceeding with the claims of USP 5,344,915. The present application claims any isolated DNA molecule encoding the novel human TBP-II protein or active fragments thereof, as well as replicable expression vehicles capable of expressing that protein, host cells transformed with such replicable expression vehicles and processes for producing the protein by culturing such host cells.

The interview graciously granted among Examiner Schwadron, the undersigned attorney, and Mr. Henry Einav, who is a representative of the exclusive licensee of the present invention, conducted on May 13, 1999, is hereby gratefully acknowledged. In this interview, the various rejections were discussed. As to the rejection in paragraph 17 of the official action of February 26, 1999, the suggestion was made that, rather than using the terminology "the N-terminal region", language be used which is better supported in the specification stating that the specified sequences are in the portion of the protein sequenced by N-terminal sequence analysis. Applicant agreed to make this change in an attempt to obviate this ground of rejection.

With respect to the rejection in paragraph 18, applicant argued that it should not be necessary to insert every possible characterizing feature from the specification in order to fingerprint a product. Once the product is adequately fingerprinted, it is not necessary to add additional characterizing data, particularly where the additional characterizing data could be subject to misconstrual in view of the fact that others had found that the same protein also appears at a higher molecular weight of about 42 to 45. The examiner was shown a publication of Corti et al, which will be discussed in more detail hereinbelow, indicating that the two molecular weights for the same protein are most likely due to differences in glycosylation pattern. The examiner indicated that he was concerned that removal of the molecular weight would

be new matter. However, applicant pointed out to the examiner that the broadest claims originally filed in this case did not include any molecular weight designation and the molecular weight was only present in a dependent claim. Whether the molecular weight is recited in the claim or not, the claims are only directed to the DNA described in the specification. The examiner indicated that he would reconsider this rejection in view of these arguments.

With respect to the rejection of paragraph 19, the issues were discussed and the examiner stated that he would continue to base his legal conclusion on what he feels is required by the interim written guidelines on 35 USC 112 written description issues in biotechnology cases. Applicant advised the examiner that in the next response a detailed analysis of these written description guidelines and their application to the present fact situation would be presented so as to show that the guidelines do indeed support applicant's interpretation.

With respect to the rejection of paragraph 21, the examiner stated that as soon as he had an opportunity to study a certified copy of the priority application, assuming that its text was the same as the non-certified copy which he had in the file, the art rejection would be withdrawn.

The arguments presented hereinbelow are offered for the consideration of the examiner in addition to those already presented at the interview.

The examiner has stated in the official action of February 26, 1999, that in the event that the claims currently

under consideration are found allowable, withdrawn claim 50 will be treated as per MPEP §821.04.

Claims 11-13 and 46-49 have been rejected under 35 USC 112, first paragraph. The examiner states that there is no support in the specification as originally filed for the recitation of "including, at the N-terminal region thereof, the amino acid sequence: ..." in claims 11 or 46. The examiner states that the specification and original claim 6 disclose that the aforementioned sequence was determined by "N-terminal sequence analysis". However, there is no support in the specification as originally filed for the use of the terminology "at the N-terminal region".

In order to obviate this rejection, the language "at the N-terminal region thereof" has now been deleted from claims 11 and 46 and instead language is used which the examiner states is supported by page 23 of the specification and claim 6 as originally filed, i.e., stating that the specified sequence is "in the portion of the protein sequenced by N-terminal sequence analysis". This is language fully supported by the specification which indicates that the specified sequence is in that part of the protein which is close to the N-terminus and thus covers the various embodiments disclosed in the specification without being unduly broad. As it is understood from the interview that the examiner will now find this language to be acceptable, this language has been inserted not only into claims 11 and 46 but also into claim 36 and new claim 51. New claim 51 is a new independent claim combining language which has

now been found acceptable from both claims 46 and 35. It is not believed that any new issues are presented by the language of claim 51 as it is of substantially the same scope as previously appearing claim 46, and all of the language therein has already appeared either in claim 35 or 46. Accordingly, no new issues are presented by claim 51 and this claim should therefore be entered either because the case is in condition for allowance or to place the case into better condition for appeal.

Accordingly, reconsideration and withdrawal of this rejection with respect to all of the claims now appearing in the case are respectfully urged.

Claims 35, 43 and 44 have been rejected under 35 USC 112, first paragraph. The examiner states that there is no support in the specification as originally filed for the claimed molecules, as the only molecule disclosed in the specification is one of 30 kD. The examiner states that applicant has not revealed where in the specification the claimed invention finds support, particularly in view of the fact that the specification states that the sequences were found upon N-terminal sequence analysis of the 30 kDa band of purified protein. The examiner states that, as there is no disclosure of any other molecular weight protein, there is no support in the specification as originally filed for a claim of the breadth of claim 35. This rejection is respectfully traversed.

As discussed at the above-mentioned interview, the protein described in the present specification has been found to exist in different molecular weight forms. For example, the

patent number 5,344,915 of LeMaire et al, which patent is involved in an interference with the protein claims appearing in the application which is the parent of the present application, discloses and claims the same protein as is claimed by the present applicants, but indicates that it has a molecular weight of about 42 kD. A copy of the LeMaire patent is attached hereto. Also attached hereto is a copy of Corti et al, "Identification of differentially glycosylated forms of the soluble p75 tumor necrosis factor (TNF) receptor in human urine", European Cytokine Network, 6:29-35 (1995). This paper reports that the two different molecular weight forms of TBP-II are caused by differences in glycosylation patterns. However, those of ordinary skill in the art will understand that the same DNA molecule will encode both as glycosylation occurs post-translationally. It is for this reason that applicant prefers not to refer to a molecular weight in defining the protein produced by the DNA of the present invention, as this could lead to some confusion in interpreting the claim in view of the fact that it is now known that the protein encoded by the same DNA might have different molecular weights.

As indicated above, there is no requirement in 35 USC 112 that a molecule which can be adequately characterized to distinguish it from all other molecules, i.e., can be "fingerprinted" by certain data from the specification, need be claimed using all possible identifying data from the specification. As long as it is sufficiently identified to distinguish it from all other molecules, there should be no

requirement to add additional data which will not further characterize the molecule. This is particularly the case here where the further data could possibly lead to ambiguities. Even without recitation of the molecular weight, the present claims adequately fingerprint the molecule of the present invention by stating that it encodes a protein having a specified 10 residue sequence in the portion of the protein sequenced by N-terminal sequence analysis and by specifying that that protein has the ability to inhibit the cytotoxic effect of TNF. The absence of the molecular weight recitation does not broaden the claim as the claim is directed to the DNA molecules disclosed in the specification, regardless of the glycosylation form which the translated protein may take. Indeed, if the DNA is expressed in a prokaryotic cell, it would be expected that the molecular weight would be altogether different.

The examiner states that there is no support in the specification for claiming the DNA without a molecular weight limitation. However, the examiner's attention is invited to claim 11 as originally filed which defines the DNA without reference to the molecular weight of the protein. Thus, a definition of the DNA which does not include molecular weight is not new matter. Claim 6 as originally filed claims the protein by the sequence obtained by N-terminal analysis and the ability of the protein to inhibit the cytotoxic effect of TNF. Therefore, it is not new matter and it is indeed supported by the specification to characterize the protein other than by reference to molecular weight. Thus, it is not new matter and

the claims which are silent as to molecular weight are supported by the specification.

For all of these reasons, it is urged that claim 51 and claim 35 and those claims dependent therefrom are adequately supported by the written description and enabling disclosure of the present specification, without reference to a specific molecular weight. The same DNA molecules are characterized regardless of whether or not the molecular weight of the protein is set forth in the claim and therefore there is no need to insert the superfluous reference to a molecular weight, particularly when it is now known that the addition of that superfluous limitation could possibly lead to some confusion in the future. Reconsideration and withdrawal of this rejection are therefore also respectfully urged.

Claims 11-13, 35-38, 43, 44 and 46-49 have been rejected under 35 USC 112, first paragraph. The examiner states that the specification does not provide adequate written description of the claimed invention as the specification does not convey to the artisan that the applicant had possession at the time of the invention of the claimed DNAs and molecules containing said DNAs. The examiner states that only nucleic acid species described in the specification meet the description requirement and that if the inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, conception has not been achieved until reduction to practice has occurred. The examiner states that here, the inventor was unable to envision the detailed

constitution of a nucleic acid so as to distinguish it from other materials because the sequence of the claimed nucleic acid was not known to the inventors at the time of the filing date of the instant application. The examiner states that the possession of an isolated protein in itself provides no written description of the identity of the nucleic acid encoding said protein in the absence of the complete amino acid sequence of the protein. This rejection is respectfully traversed.

Applicant respectfully urges that the examiner has erred in stating that the detailed constitution of the nucleic acids of the present invention are insufficiently disclosed so as to distinguish it from other materials. It is urged that the facts of the present case distinguish it from the cases such as University of California v. Eli Lilly, Amgen v. Chugai and Fiers v. Revel, cited or referred to by the examiner. Indeed, it is urged that the interim guidelines for examination of patent applications under the 35 USC 112, paragraph 1 "Written Description" requirement mandate withdrawal of this rejection.

The interim guidelines referred to by the examiner appear at Federal Register, Volume 43, No. 114, of June 15, 1998, at pages 32639-32645. Section I.C. of the guidelines states:

For each claimed species, determine whether there is sufficient written description to inform a skilled artisan that applicant was in possession of the claimed invention at the time the application was filed.

In this section, two criteria are set forth. Criteria C(1) states:

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One example given in the guidelines as representing a claim which fulfills the written description requirement of 35 USC 112, first paragraph, is the following:

For example, consider the following claim:

An isolated double-stranded DNA consisting of (1) a single-stranded DNA which has a molecular size of 2.57 Kb and is derived from golden mosaic virus, and (2) a DNA complimentary to said single-stranded DNA, giving the restriction and/or nuclease cleavage map shown in Fig. 2(a) and having no Nbo I restriction and/or nuclease site.

Although the specification does not disclose the complete structure for the claimed DNA, it does disclose sufficient identifying characteristics, i.e., size, cleavage map, and source from which the DNA is derived. Thus, while this claim does not meet the C(1) criteria because the complete sequence is not disclosed, it does meet the C(2) criteria because one skilled in the art would recognize from the characteristics, e.g., size, map, source, that applicant was in possession of the claimed material at the time of filing.

This example should put to rest the notion that a DNA claim can never be considered to be sufficiently described without the full nucleotide sequence. Thus, the only question that need be answered here is whether the identifying characteristics of the present claims are sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention.

The present claims characterize the DNA as encoding a specified protein which protein is sufficiently described to uniquely identify it. It is believed that there is no dispute that the specification sufficiently describes the named protein in order to uniquely identify it. This is evidenced by the fact that at least one allowed protein claim appears in parent application 07/930,443, which is presently in an interference proceeding. It should be noted that the interim guidelines indicate that the same criteria exist for DNA as exist for protein. Indeed, a second example of claiming a species under guideline C(2) relates to the claiming of a protein without specifying a sequence other than an N-terminal amino acid sequence. This example relates to the following claim:

An isolated alginate lyase enzyme wherein said enzyme lyses alginate in the mucous substance produced in a patient with cystic fibrosis and wherein said enzyme has the N-terminal amino acid sequence of SEQ ID NO:1, obtained from *Flavobacterium pepermentium* and has the following physico-chemical properties: ... .

With respect to this claim, the guidelines state:

In this example, the specification discloses the molecular weight, origin, activity, and specificity but does not disclose the complete structure for the claimed enzyme. Thus, this claim would not meet the C(1) criteria because the complete sequence is not disclosed. However, the claim meets the C(2) criteria because, although the complete structure is not disclosed, one skilled in the art would recognize from the disclosed physical characteristics - e.g., molecular weight, origin, activity, and specificity - that applicant was in possession of the claimed material at the time of filing.

Thus, it is perfectly consistent with the interim written description guidelines to hold that the protein meets the C(2) criteria because, although the complete structure is not disclosed, one skilled in the art would recognize from the disclosed physical characteristics that applicant was in possession of the claimed material at the time of filing. If one was in possession of the protein at the time the present application was filed, then one must necessarily also be in possession of the DNA as the DNA is as uniquely described as the protein since the structure of the DNA necessarily follows from the genetic code table from the knowledge of the protein.

The examiner states that there is not sufficient written description of the DNA as the possession of an isolated protein in itself provides no written description of the identity of the nucleic acid encoding said protein in the absence of the complete amino acid sequence of said protein. In this regard, however, it should be understood that the present claims differ from the claims in University of California v. Eli Lilly, Amgen v. Chugai and Fiers v. Revel in that in each of those cases the claims were directed to a specific cDNA of a single specific sequence. Here, however, the claims are directed to any DNA which encodes the protein which is uniquely identified in the present specification. Therefore, it is not necessary to provide identifying characteristics of a specific DNA sequence, but it is only necessary to provide identifying characteristics of the protein sufficient to characterize it and distinguish it from other materials.

Just as a DNA can fully meet the written description requirement of the first paragraph of 35 USC 112, despite a lack of disclosure of the complete structure, as long as sufficient identifying characteristics are present, so too a protein can be described in a manner which complies with the first paragraph of 35 USC 112, despite the absence of the complete amino acid structure thereof, if other identifying characteristics are present. Here, there is no dispute that there are sufficient identifying characteristics of the protein even though these identifying characteristics do not include the complete amino acid structure. In view of the fact that the present claims are directed to any nucleic acid which encodes this protein, the DNA of the present invention is necessarily identified for the same reason that the protein is identified.

Furthermore, the claims effectively contain a partial nucleic acid sequence. All of the present claims contain at least 10 amino acid residues of the protein encoded by the DNA. Thus, at least 30 nucleotides of the DNA are disclosed. Regardless of the fact that the DNA molecule of the present invention is much longer than 30 nucleotides, this is an important unique bit of characterizing information. This piece of nucleotide structure, in conjunction with the characterizing information that the DNA encodes a protein having the ability to inhibit the cytotoxic effects of TNF, provides sufficient relevant identifying characteristics to comply with criteria C(2) of the interim guidelines.

The interim guidelines also provide an example of a claim which does not comply with the written description requirement of 35 USC 112. This claim reads:

An isolated nucleotide sequence consisting of the sequence of the reverse transcript of a human mRNA, which mRNA encodes insulin.

This theoretical claim is supported by a theoretical specification which provides the coding sequence for rat insulin, but not that for human insulin. The guidelines conclude:

A sequence described only by a *purely* functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed species. In this case, even though a genetic code table would correlate a known insulin amino acid sequence with a genus of coding amino acids, the same table cannot predict the native, naturally occurring nucleic acid sequence of human mRNA or its corresponding cDNA. Thus, the specification in this example does not provide adequate written description, either under the C(1) or C(2) criteria. [Emphasis original]

The present situation is not a case in which the sequence is described only by a purely functional characteristic without any known or disclosed correlation between that function and the structure. Here, the situation is much closer to that of the claim which was found to be satisfactorily described. The guidelines emphasize with respect to this example that, even if the entire amino acid sequence of the encoded protein were

known, one would not be able to predict the native naturally occurring nucleic acid sequence of the human mRNA or its corresponding cDNA until it was actually obtained. Here, however, as indicated above, applicant is not claiming a specific naturally occurring nucleic acid sequence of a human mRNA or its corresponding cDNA. Applicant is claiming all nucleotide sequences which, through a genetic code table, would correlate to the amino acid sequence of the encoded protein which has been sufficiently described in the specification to allow it to be claimed in the manner which is fully supported by the written description requirement of 35 USC 112. Therefore, the present situation is clearly distinguishable from the example in the guidelines which was found to be unacceptable. It should be noted that this latter situation is exactly that situation presented in University of California v. Eli Lilly relied upon by the examiner. Thus, the present fact situation is distinguishable from the University of California v. Eli Lilly fact situation for the same reasons as discussed above with respect to this example of the interim guidelines.

Accordingly, (1) since the interim guidelines clearly provide that it is possible for a claim to a DNA molecule to comply with the written description requirement of 35 USC 112, paragraph 1, despite of a lack of disclosure of a complete nucleotide structure, and (2) in view of the fact that it has been conceded that the written description of the present specification provides sufficient identifying characteristics to provide written description support for a claim to the protein

encoded by the nucleic acid of the DNA of the present claims, and (3) in view of the fact that anyone with a genetic code table could correlate the nucleic acid structure of the presently claimed DNA with the amino acid structure of the protein which is adequately described in the present specification, i.e., the present claims are not directed to a unique cDNA but cover any sequence which encodes the protein, the conclusion must be reached that, just as sufficient identifying characteristics are present for the protein, so, too, sufficient identifying characteristics are present for the DNA. Since the guidelines indicate that the same criteria are applied to proteins and to DNA, the fact that the protein is sufficiently identified, must lead to the conclusion in this case that the DNA is also sufficiently identified. Furthermore, the fact that the claim effectively has a partial DNA sequence which further distinguishes the DNA of the present invention from all other DNA, which is effectively independent from the other characteristics which relate only to the protein encoded by the DNA, the conclusion must be reached that the C(2) criteria of the interim guidelines have been met. Accordingly, by the very guidelines which the examiner professes to be following, the conclusion must be reached that all of the present claims are adequately supported by the written description of the present specification so as to comply with the written description requirement of the first paragraph of 35 USC 112. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 11-13, 35-38, 43, 44 and 46-49 remain rejected under 35 USC 102(e) as being anticipated by Smith. The examiner states that this rejection can be overcome by the submission of English-language copies of the foreign priority documents, assuming that the claimed inventions are disclosed in said foreign priority documents. The examiner states that he has not been able to find certified copies of the foreign priority documents in the parent application. This rejection is respectfully traversed.

Attached hereto is a copy of applicant's transmittal letter of May 16, 1990, submitted upon filing of applicant's grandparent application no. 07/524,263. The first paragraph of this letter states that certified copies of the Israeli applications for which priority is claimed were attached thereto. Furthermore, attached hereto is a copy of the cover sheet of the official action of March 19, 1992, in application no. 07/524,263, in which the examiner in paragraph 12 has checked off the box indicating that acknowledgment is made of the claim for priority under 35 USC 119 and receipt of the certified copy. Accordingly, the Patent and Trademark Office record shows that the certified copy of the priority document was filed. Applicant has no obligation to submit another certified copy if the Patent and Trademark Office loses the original.

Nevertheless, applicant is now in the process of procuring additional certified copies of these applications from the Israel Patent Office. As soon as they are received, they

will be submitted to the examiner so that the examiner can fully satisfy himself that the present claims are supported at least by the earliest of these, i.e., Israel application 90,339 filed May 18, 1989, thus obviating this rejection. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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